November 6, 1946.

Dear Sol:

How's the Genius? (That is Loewi's description; I heard it with my own ears this summer at Woods Hole.)

Bonner just let me see a copy of your manuscript, and reading it was just like being at Cold Spring Harbour, hearing one line of evidence after another until one is almost compelled to say:Stop, I'll believe anything you say. It is quite thrilling. Anything new?

There is only one point which is not quite clear to me, and that is the detail of the postulated mechanism of substrate-enzyme interactions, particularly between different systems. What, do you propose is the mechanism by which the formation of a second enzyme depletes the first ; why should the presence of exogenous N affect this process if the substrates are simply competing on unstable enzyme molecules? Why are the enzymes less unstable in the presence of azide? All of these questions are based on this conception of the role of substrate: that the precursor suffers random reversible changes, occasionally producing enzymatically specific molecules, and that these are stabilized by the presence of the substrate. However, it is difficult for me to see the role of a second 'competing substrate' in effecting changes in the rate of the reaction of decomposition from E to Pr. Perhaps this is too simplified a conception; I would appreciate it if you could clarify it for me. You may be interested that a preliminary note on our bacterial work has appeared in Nature for Oct. 19. I'm climbing on your bandwagon, in a way; in hopes of finding non Mendelian

mechanisms to account for certain discrepancies in the ratios of the various new types that appear in our mixed cultures, we are going to look at the inheritance of a lactose fermentation character; E. coli (a triple mtant Y-10) was heavily irradiated, and after preliminary cultivation, was spread out on EMB-lactose plates. 1/ 20,000 colonies was a non-fermenter, and we are going to study the segregation of this character into prototrophs when Y-10-L- and another biochemical mutant/ which is Lplus are crossed, in the presence and absence of lactose. Any suggestions?

Well, best of luck, and regards to everybody there,

Sincerely,

Josh.